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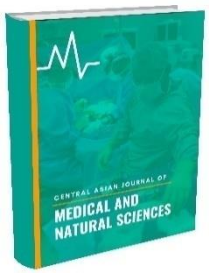

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BIOCHEMICAL MECHANISMS OF THE BREAKDOWN OF COMPLEX MOLECULES IN THE BODY

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Annotation: *There are two main reasons for studying a metabolic pathway: (1) to describe, in quantitative terms, the chemical changes catalyzed by the component enzymes of the route; and (2) to describe the various intracellular controls that govern the rate at which the pathway functions.*

Key words: Metabolic pathway, organism, enzyme, acis, DNA, tissue.

Studies with whole organisms or organs can provide information that one substance is converted to another and that this process is localized in a certain tissue; for example, experiments can show that urea, the chief nitrogen-containing end product of protein metabolism in mammals, is formed exclusively in the liver. They cannot reveal, however, the details of the enzymatic steps involved. Clues to the identity of the products involved, and to the possible chemical changes effected by component enzymes, can be provided in any of four ways involving studies with either whole organisms or tissues.

First, under stress or the imbalances associated with diseases, certain metabolites may accumulate to a greater extent than normal. Thus, during the stress of intense exercise, lactic acid appears in the blood, while glycogen, the form in which carbohydrate is stored in muscle, disappears. Such observations do not, however, prove that lactic acid is a normal intermediate of glycogen catabolism; rather, they show only that compounds capable of yielding lactic acid are likely to be normal intermediates. Indeed, in the example, lactic acid is formed in response to abnormal circumstances and is not directly formed in the pathways of carbohydrate catabolism.

Second, the administration of metabolic poisons may lead to the accumulation of specific metabolites. If fluoroacetic acid or fluorocitric acid is ingested by animals, for example, citric acid accumulates in the liver. This correctly suggests that fluorocitric acid administered as such, or formed from fluoroacetic acid via the tricarboxylic acid (TCA) cycle, inhibits an enzyme of citrate oxidation.

Third, the fate of any nutrient—indeed, often the fate of a particular chemical group or atom in a nutrient—can be followed with relative ease by administering the nutrient labeled with an isotope. Isotopes are forms of an element that are chemically indistinguishable from each other but differ in physical properties.

The use of a nonradioactive isotope of nitrogen in the 1930s first revealed the dynamic state of body constituents. It had previously been believed that the proteins of tissues are stable once formed, disappearing only with the death of the cell. By feeding amino acids labeled with isotopic nitrogen to rats, it was discovered that the isotope was incorporated into many of the amino acids found in proteins of the liver and the gut, even though the total protein content of these tissues did not change. This suggested that the proteins of these tissues exist in a dynamic steady state, in which relatively high rates of synthesis are counterbalanced by equal rates of degradation. Thus, although the average liver cell has a life-span of several months, half of its proteins are synthesized and degraded every five to six days. On the other hand, the proteins of the muscle or the brain, tissues that (unlike the gut or liver) need not adjust to changes in the chemical composition of their milieu, do not turn over as rapidly. The high rates of turnover observed in liver and gut tissues indicate that the coarse controls, exerted through the onset and cessation of synthesis of pacemaker enzymes, do occur in animal cells.

Finally, genetically altered organisms (mutants) fail to synthesize certain enzymes in an active form. Such defects, if not lethal, result in the accumulation and excretion of the substrate of the defective enzyme; in normal organisms, the substrate would not accumulate, because it would be acted upon by the enzyme. The significance of this observation was first realized in the early 20th century when the phrase "inborn errors of metabolism" was used to describe hereditary conditions in which a variety of amino acids and other metabolites are excreted in the urine. In microorganisms, in which it is relatively easy to cause genetic mutations and to select specific mutants, this technique has been very useful. In addition to their utility in the unraveling of metabolic pathways, the use of mutants in the early 1940s led to the postulation of the one gene-one enzyme hypothesis by the Nobel Prize winners George W. Beadle and Edward L. Tatum; their discoveries opened the field of biochemical genetics and first revealed the nature of the fine controls of metabolism.

Because detailed information about the mechanisms of component enzymatic steps in any metabolic pathway cannot be obtained from studies with whole organisms or tissues, various techniques have been developed for studying these processes—e.g., sliced tissues, and homogenates and cell-free extracts, which are produced by physical disruption of the cells and the removal of cell walls and other debris. The sliced-tissue technique was successfully used by the Nobel Prize winner Sir Hans Krebs in his pioneer studies in the early 1930s on the mechanism of urea formation in the liver. Measurements were made of the stimulating effects of small quantities of amino acids on both the rate of oxygen uptake and the amount of oxygen taken up; the amino acids were added to liver slices bathed in a nutrient medium. Such measurements revealed the cyclic nature of the process; specific amino acids acted as catalysts, stimulating respiration to an extent greater than expected from the quantities added. This was because the added material had been re-formed in the course of the cycle (*see below* Disposal of nitrogen).

Homogenates of tissue are useful in studying metabolic processes because permeability barriers that may prevent ready access of external materials to cell components are destroyed. The tissue is usually minced, blended, or otherwise disrupted in a medium that is suitably buffered to maintain the normal acid–base balance of the tissue, and contains the ions required for many life processes, chiefly sodium, potassium, and magnesium. The tissue is either used directly—as was done by Krebs in elucidating, in 1937, the TCA cycle from studies of the respiration of minced pigeon breast muscle—or fractionated (i.e., broken down) further. If the latter procedure is followed, homogenization is often carried out in a medium containing a high concentration of the sugar sucrose, which provides a milieu favourable for maintaining the integrity of cellular components. The components are recovered by careful spinning in a centrifuge, at a series of increasing speeds. It is thus possible to obtain fractions containing predominantly one type of organelle: nuclei (and some unbroken cells); mitochondria, lysosomes, and microbodies; microsomes (i.e., ribosomes and endoplasmic reticulum fragments); and—after prolonged centrifugation at forces in excess of 100,000 times gravity—a clear liquid that represents the soluble fraction of the cytoplasm. The fractions thus obtained can be further purified and tested for their capacity to carry out a given metabolic step or steps. This procedure was used to show that isolated mitochondria catalyze the oxidation reactions of the TCA cycle and that these organelles also contain the enzymes of fatty acid oxidation. Similarly, isolated ribosomes are used to study the pathway and mechanism of protein synthesis.

The final step in elucidating a reaction in a metabolic pathway includes isolation of the enzyme involved. The rate of the reaction and the factors that control the activity of the enzyme are then measured.

It should be emphasized that biochemists realize that studies on isolated and highly purified systems, such as those briefly described above, can do no more than approximate biological reality. The identification of the fine and coarse controls of a metabolic pathway, and (when appropriate) other influences on that pathway, must ultimately involve the study of the pathway in the whole cell or organism. Although some techniques have proved adequate for relating findings in the test tube to the situation in living organisms, study of the more complex metabolic processes, such as those involved in differentiation and development, may require the elaboration of new experimental approaches.

Food materials must undergo oxidation in order to yield biologically useful energy. Oxidation does not necessarily involve oxygen, although it must involve the transfer of electrons from a donor molecule to a suitable acceptor molecule; the donor is thus oxidized and the recipient reduced. Many microorganisms either must live in the absence of oxygen (i.e., are obligate anaerobes) or can live in its presence or its absence (i.e., are facultative anaerobes).

If no oxygen is available, the catabolism of food materials is effected via fermentations, in which the final acceptor of the electrons removed from the nutrient is some organic molecule, usually generated during the fermentation process. There is no net oxidation of the food molecule in this type of catabolism; that is, the overall oxidation state of the fermentation products is the same as that of the starting material.

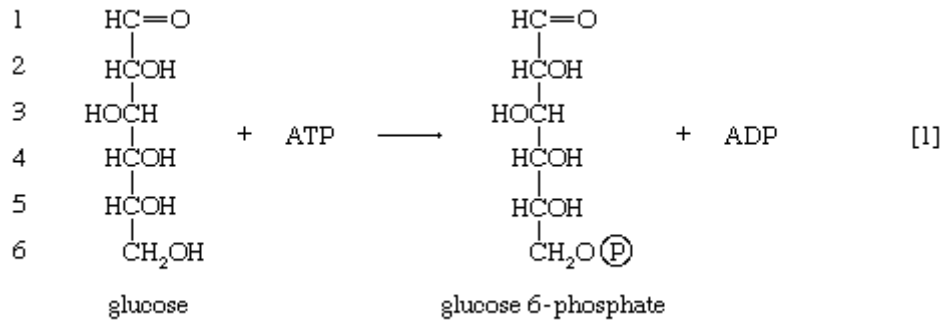
Organisms that can use oxygen as a final electron acceptor also use many of the steps in the fermentation pathways in which food molecules are broken down to smaller fragments; these fragments, instead of serving as electron acceptors, are fed into the TCA cycle, the pathway of terminal respiration.

In this cycle all of the hydrogen atoms (H) or electrons (e^-) are removed from the fragments and are channeled through a series of electron carriers, ultimately to react with oxygen (O; *see below* Energy conservation). All carbon atoms are eliminated as carbon dioxide (CO_2) in this process. The sequence of reactions involved in the catabolism of food materials may thus be conveniently considered in terms of an initial fragmentation (fermentation), followed by a combustion (respiration) process.

Quantitatively, the most important source of energy for cellular processes is the six-carbon sugar glucose ($C_6H_{12}O_6$). Glucose is made available to animals through the hydrolysis of polysaccharides, such as glycogen and starch, the process being catalyzed by digestive enzymes. In animals, the sugar thus set free passes from the gut into the bloodstream and from there into the cells of the liver and other tissues. In microorganisms, of course, no such specialized tissues are involved.

The fermentative phase of glucose catabolism (glycolysis) involves several enzymes; the action of each is summarized below. In living cells, many of the compounds that take part in metabolism exist as negatively charged moieties, or anions, and are named as such in most of this article (e.g., pyruvate, oxaloacetate).

In order to obtain a net yield of ATP from the catabolism of glucose, it is first necessary to invest ATP. During step [1] the alcohol group at position 6 of the glucose molecule readily reacts with the terminal phosphate group of ATP, forming glucose 6-phosphate and ADP. For convenience, the phosphoryl group (PO_3^{2-}) is represented by Ⓟ. Because the decrease in free energy is so large, this reaction is virtually irreversible under physiological conditions.

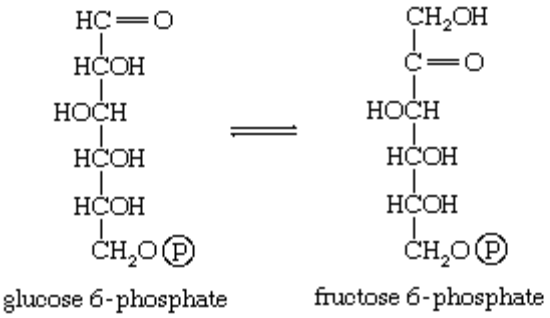


In animals, this phosphorylation of glucose, which yields glucose 6-phosphate, is catalyzed by two different enzymes. In most cells a hexokinase with a high affinity for glucose—i.e., only small amounts of glucose are necessary for enzymatic activity—effects the reaction. In addition, the liver contains a glucokinase, which requires a much greater concentration of glucose before it reacts. Glucokinase functions only in emergencies, when the concentration of glucose in the blood rises to abnormally high levels.

Certain facultative anaerobic bacteria also contain hexokinases but apparently do not use them to phosphorylate glucose. In such cells, external glucose can be utilized only if it is first phosphorylated to glucose 6-phosphate via a system linked to the cell membrane that involves a compound called

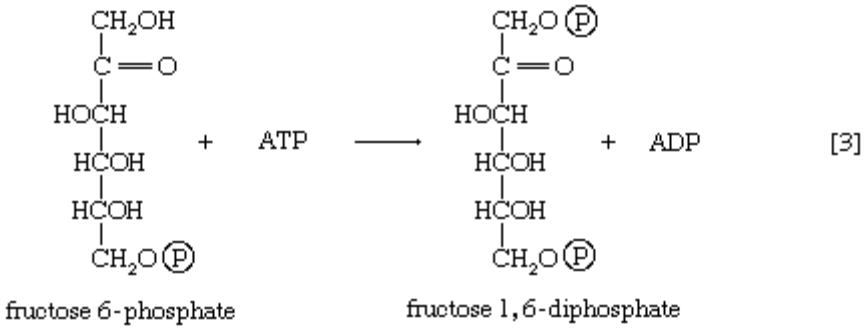
phosphoenolpyruvate (formed in step [9] of glycolysis), which serves as an obligatory donor of the phosphate group; i.e., ATP cannot serve as the phosphate donor in the reaction.

The reaction in which glucose 6-phosphate is changed to fructose 6-phosphate is catalyzed by phosphoglucoisomerase [2]. In the reaction, a secondary alcohol group (—C|HOH) at the second carbon atom is oxidized to a keto-group (i.e., —C|=O), and the aldehyde group (—CHO) at the first carbon atom is reduced to a primary alcohol group (—CH_2OH). Reaction [2] is readily reversible, as is indicated by the double arrows.



[2]

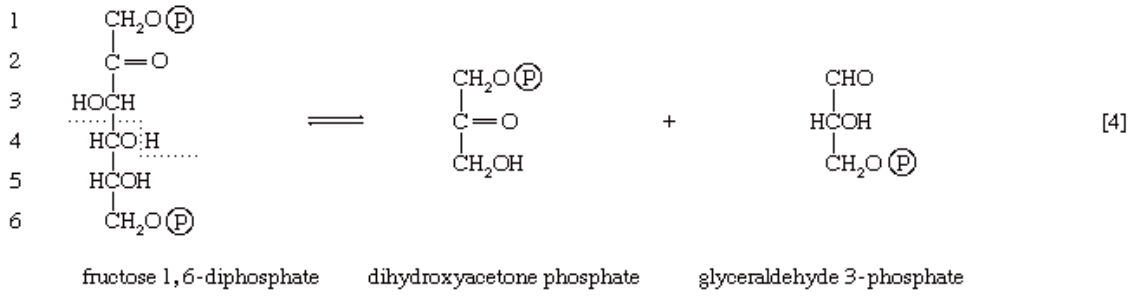
The formation of the alcohol group at the first carbon atom permits the repetition of the reaction effected in step [1]; that is, a second molecule of ATP is invested. The product is fructose 1,6-diphosphate [3]. Again, as in the hexokinase reaction, the decrease in free energy of the reaction, which is catalyzed by phosphofructokinase, is sufficiently large to make this reaction virtually irreversible under physiological conditions; ADP is also a product.



[3]

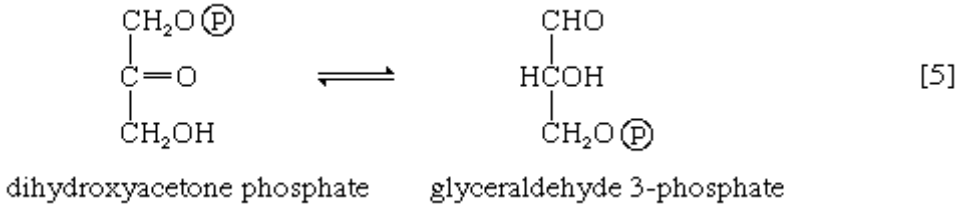
The first three steps of glycolysis have thus transformed an asymmetrical sugar molecule, glucose, into a symmetrical form, fructose 1,6-diphosphate, containing a phosphoryl group at each end; the molecule next is split into two smaller fragments that are interconvertible. This elegant simplification is

achieved via steps [4] and [5], which are described below.



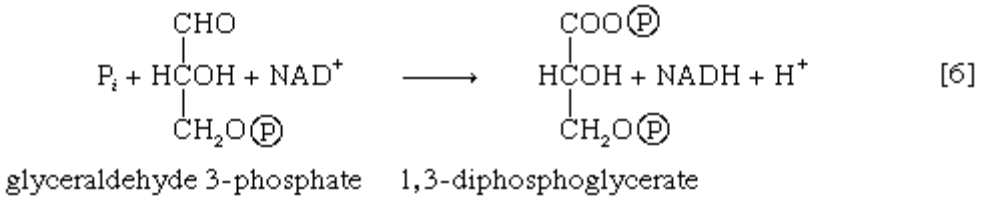
The aldolase reaction

In [4], an enzyme catalyzes the breaking apart of the six-carbon sugar fructose 1,6-diphosphate into two three-carbon fragments. The molecule is split between carbons 3 and 4. Reversal of this cleavage—i.e., the formation of a six-carbon compound from two three-carbon compounds—is possible. Because the reverse reaction is an aldol condensation—i.e., an aldehyde (glyceraldehyde 3-phosphate) combines with a ketone (dihydroxyacetone phosphate)—the enzyme is commonly called aldolase. The two three-carbon fragments produced in step [4], dihydroxyacetone phosphate and glyceraldehyde 3-phosphate, are also called triose phosphates. They are readily converted to each other by a process [5] analogous to that in step [2]. The enzyme that catalyzes the interconversion [5] is triose phosphate isomerase, an enzyme different from that catalyzing step [2].



The formation of ATP

The second stage of glucose catabolism comprises reactions [6] through [10], in which a net gain of ATP is achieved through the oxidation of one of the triose phosphate compounds formed in step [5]. One molecule of glucose forms two molecules of the triose phosphate; both three-carbon fragments follow the same pathway, and steps [6] through [10] must occur twice to complete the glucose

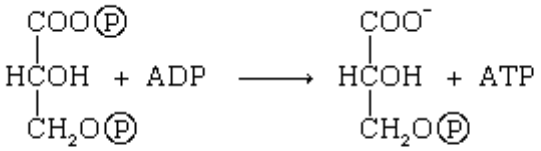


breakdown.

Step [6], in which glyceraldehyde 3-phosphate is oxidized, is one of the most important reactions in glycolysis. It is during this step that the energy liberated during oxidation of the aldehyde group (—CHO) is conserved in the form of a high-energy phosphate compound—namely, as 1,3-diphosphoglycerate, an anhydride of a carboxylic acid and phosphoric acid. The hydrogen atoms or electrons removed from the aldehyde group during its oxidation are accepted by a coenzyme (so called

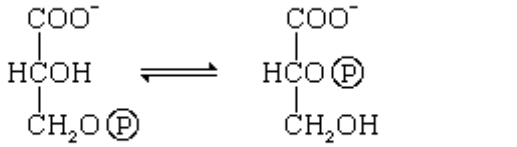
because it functions in conjunction with an enzyme) involved in hydrogen or electron transfer. The coenzyme, nicotinamide adenine dinucleotide (NAD^+), is reduced to form NADH + H^+ in the process. The NAD^+ thus reduced is bound to the enzyme glyceraldehyde 3-phosphate dehydrogenase, catalyzing the overall reaction, step [6].

The 1,3-diphosphoglycerate produced in step [6] reacts with ADP in a reaction catalyzed by phosphoglycerate kinase, with the result that one of the two phosphoryl groups is transferred to ADP to form ATP and 3-phosphoglycerate. This reaction [7] is highly exergonic (i.e., it proceeds with a loss of free energy); as a result, the oxidation of glyceraldehyde 3-phosphate, step [6], is irreversible. In summary, the energy liberated during oxidation of an aldehyde group (—CHO in glyceraldehyde 3-phosphate) to a carboxylic acid group (—COO^- in 3-phosphoglycerate) is conserved as the phosphate bond energy in ATP during steps [6] and [7]. This step occurs twice for each molecule of glucose. Thus, the initial investment of ATP in steps [1] and [3] is recovered.



[7]

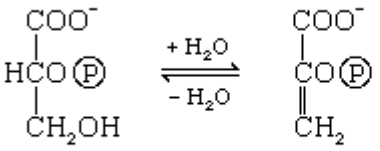
1,3-diphosphoglycerate 3-phosphoglycerate



[8]

3-phosphoglycerate 2-phosphoglycerate

The 3-phosphoglycerate in step [7] now forms 2-phosphoglycerate in a reaction catalyzed by phosphoglyceromutase [8]. During step [9] the enzyme enolase reacts with 2-phosphoglycerate to form phosphoenolpyruvate (PEP), water being lost from 2-phosphoglycerate in the process. Phosphoenolpyruvate acts as the second source of ATP in glycolysis. The transfer of the phosphate group from PEP to ADP, catalyzed by pyruvate kinase [10], is also highly exergonic and is thus virtually irreversible under physiological conditions.

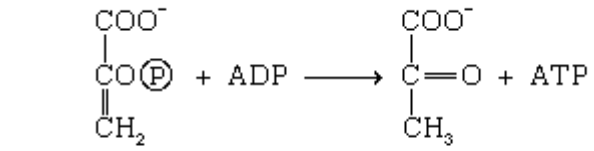


[9]

2-phosphoglycerate phosphoenolpyruvate

Reaction [10] occurs twice for each molecule of glucose entering the glycolytic sequence. Thus, the net yield is two molecules of ATP for each six-carbon sugar. No further molecules of glucose can enter the glycolytic pathway, however, until the NADH + H^+ produced in step [6] is reoxidized to NAD^+. In anaerobic systems this means that electrons must be transferred from (NADH + H^+) to some organic

acceptor molecule, which thus is reduced in the process. Such an acceptor molecule could be the

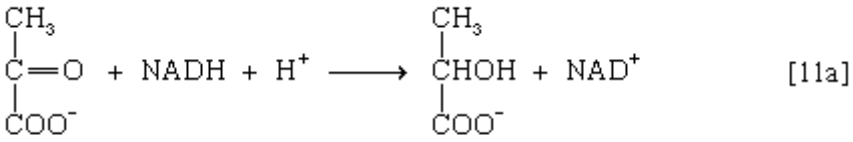


[10]

phosphoenolpyruvate pyruvate

pyruvate formed in reaction [10].

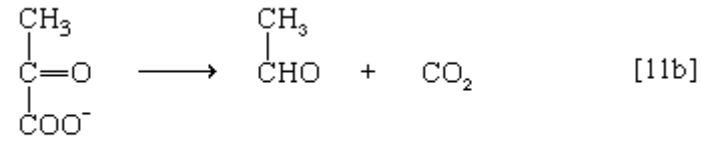
In certain bacteria (e.g., so-called lactic acid bacteria) or in muscle cells functioning vigorously in the absence of adequate supplies of oxygen, pyruvate is reduced to lactate via a reaction catalyzed by lactate dehydrogenase (reaction 11a]); i.e., NADH gives up its hydrogen atoms or electrons to pyruvate, and lactate and NAD^+ are formed.



[11a]

pyruvate lactate

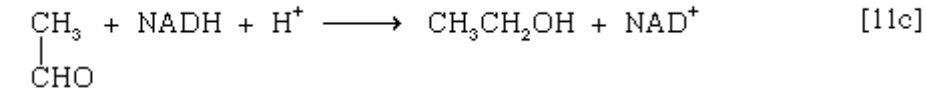
Alternatively, in organisms such as brewers' yeast, pyruvate is first decarboxylated to form acetaldehyde and carbon dioxide in a reaction catalyzed by pyruvate decarboxylase [11b].



[11b]

pyruvate acetaldehyde

Acetaldehyde then is reduced (by NADH + H^+) in a reaction catalyzed by alcohol dehydrogenase [11c], yielding ethanol and oxidized coenzyme (NAD^+).



[11c]

acetaldehyde ethanol

Many variations of reactions [11a, b, and c] occur in nature. In the heterolactic (mixed lactic acid) fermentations carried out by some microorganisms, a mixture of reactions [11a, b, and c] regenerates NAD^+ and results in the production, for each molecule of glucose fermented, of a molecule each of lactate, ethanol, and carbon dioxide. In other types of fermentation, the end products may be derivatives of acids such as propionic, butyric, acetic, and succinic; decarboxylated materials derived from them (e.g., acetone); or compounds such as glycerol.

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